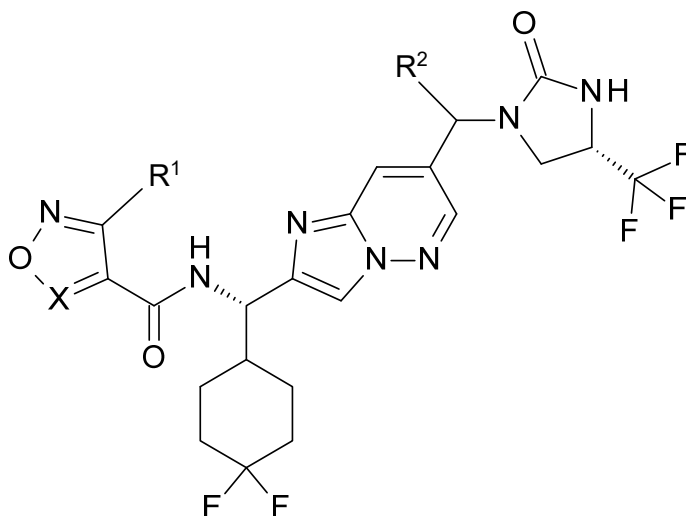


Summary

In one aspect of the present disclosure, there is provided a compound of the formula:



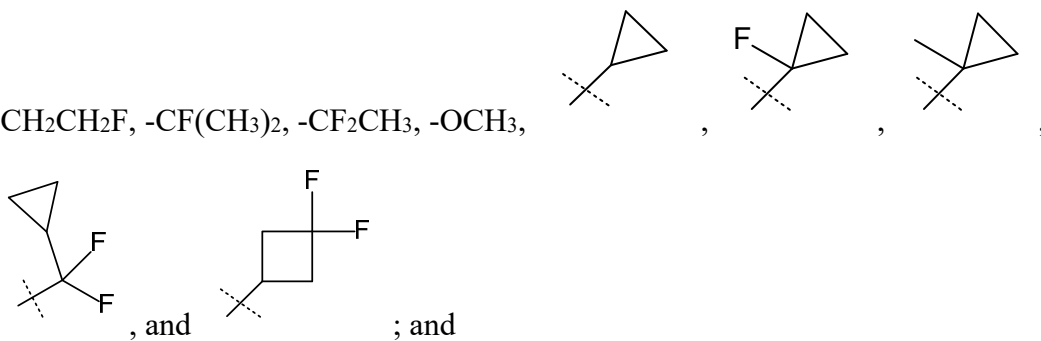
wherein:

5

X is CH, or N;

R¹ is -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₃, -CH₂CF₃, -CH(CH₃)₂, -CH₂CHF₂,

-CH₂CH₂F, -CF(CH₃)₂, -CF₂CH₃, -OCH₃,



R² is -H or -CH₂OCH₃;

10

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.

5 In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.

In another another aspect of the present disclosure, there is provided a use of N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methyl-1,2,5-oxadiazole-3-carboxamide,
10 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

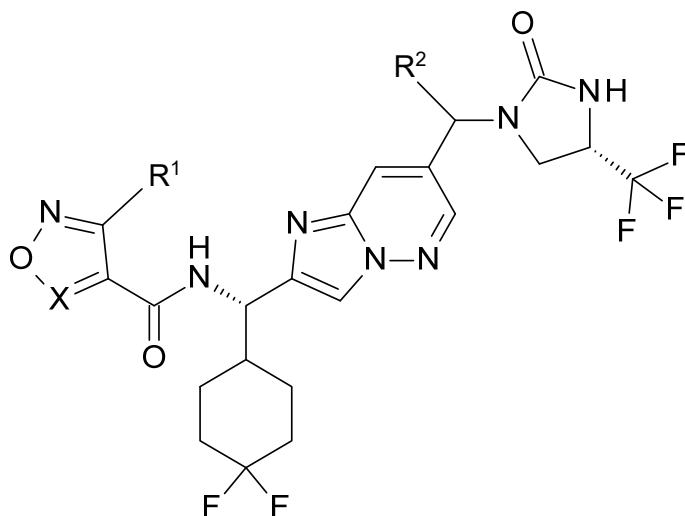
15 In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder selected from the group consisting of psoriasis, rheumatoid arthritis, spondyloarthritis, multiple sclerosis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis, hidradenitis suppurativa, systemic lupus erythematosus, palmoplantar pustulosis (PPP), atopic dermatitis, asthma, and/or COPD.

20 In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of psoriasis

In another aspect of the present disclosure, there is provided a compound of N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methyl-1,2,5-oxadiazole-3-carboxamide,
25 or a pharmaceutically acceptable salt thereof, for use in treating psoriasis.

Description

The present invention provides a compound of formula II:



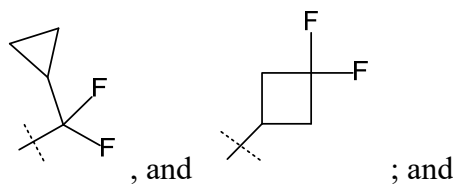
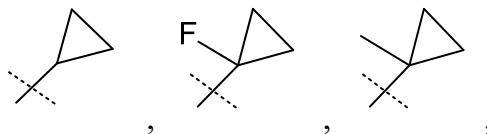
(II)

5 wherein:

X is CH, or N;

R¹ is -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₃, -CH₂CF₃, -CH(CH₃)₂, -CH₂CHF₂,

-CH₂CH₂F, -CF(CH₃)₂, -CF₂CH₃, -OCH₃,

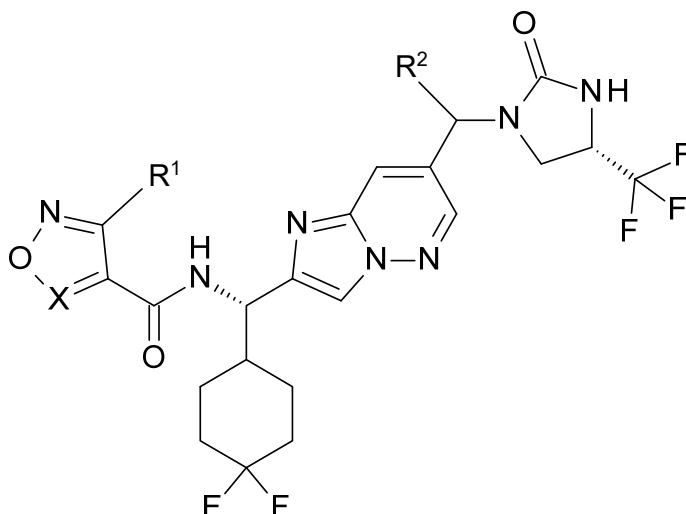


, and ; and

10 R² is -H or -CH₂OCH₃;

We claim:

1. A compound of the formula:



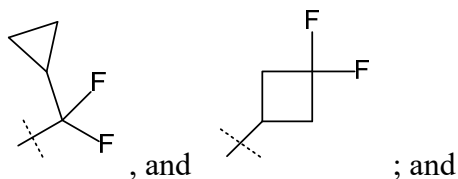
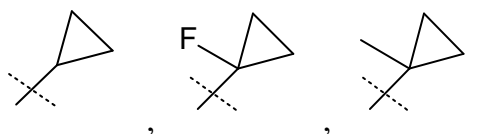
wherein:

5

X is CH, or N;

R¹ is -CH₃, -CH₂F, -CHF₂, -CF₃, -CH₂CH₃, -CH₂CF₃, -CH(CH₃)₂, -CH₂CHF₂,

-CH₂CH₂F, -CF(CH₃)₂, -CF₂CH₃, -OCH₃,



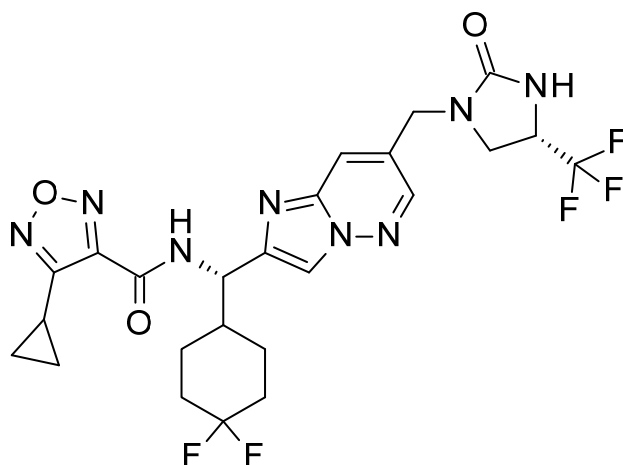
R² is -H or -CH₂OCH₃;

10

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein X is CH, or a pharmaceutically acceptable salt thereof.
3. The compound according to claim 1 wherein X is N, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 2 or 3 wherein R² is -CH₂OCH₃, or a pharmaceutically acceptable salt thereof.
5. The compound according to claim 3 of the formula:



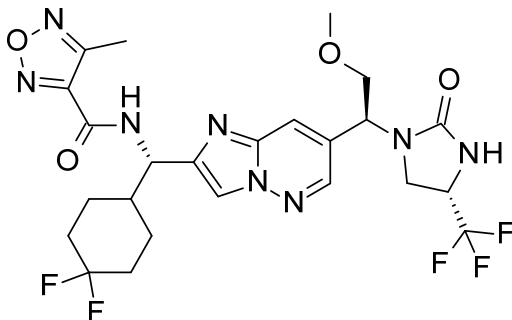
5

or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 5 which is crystalline 4-cyclopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-1,2,5-oxadiazole-3-carboxamide; ethanesulfonic acid.
7. The compound of Claim 6 which is crystalline 4-cyclopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-1,2,5-oxadiazole-3-carboxamide; ethanesulfonic acid characterized by an X-ray powder diffraction pattern using CuK α radiation having a diffraction peak at diffraction angle 2-theta of 19.2 in combination with one or more of the peaks selected from the group consisting of 19.7, 6.5, and 8.4; with a tolerance for the diffraction angles of 0.2 degrees.

20

8. The compound according to claim 4 of the formula:



or a pharmaceutically acceptable salt thereof.

- 5 9. The compound of Claim 8 which is crystalline N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methyl-1,2,5-oxadiazole-3-carboxamide; hemi-ethane-1,2-disulfonic acid.
- 10 10. The compound of Claim 9 which is crystalline N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methyl-1,2,5-oxadiazole-3-carboxamide; hemi-ethane-1,2-disulfonic acid characterized by an X-ray powder diffraction pattern using CuK α radiation having a diffraction peak at diffraction angle 2-theta of 17.1 in combination with one or more of the peaks selected from the group consisting of 7.6, 19.4, and 10.7; with a tolerance for the diffraction angles of 0.2 degrees.
11. The compound of claim 1 selected from the group consisting of:
20 3-cyclopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]isoxazole-4-carboxamide;

- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-ethyl-isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-methyl-isoxazole-4-carboxamide;
- 5 N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(difluoromethyl)isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(1,1-difluoroethyl)isoxazole-4-
- 10 carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(fluoromethyl)isoxazole-4-
- carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(2,2-difluoroethyl)isoxazole-4-
- 15 carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(2-fluoroethyl)isoxazole-4-
- carboxamide;
- 20 3-(3,3-difluorocyclobutyl)-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(trifluoromethyl)isoxazole-4-
- 25 carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(1-fluorocyclopropyl)isoxazole-4-
- carboxamide;

- 3-[cyclopropyl(difluoro)methyl]-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]isoxazole-4-carboxamide;
- 5 N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(1-methylcyclopropyl)isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-(1-fluoro-1-methylethyl)isoxazole-4-carboxamide;
- 10 N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-3-isopropyl-isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-ethyl-1,2,5-oxadiazole-3-
- 15 carboxamide;
- 4-isopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-1,2,5-oxadiazole-3-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methoxy-1,2,5-oxadiazole-3-
- 20 carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-(2,2,2-trifluoroethyl)-1,2,5-oxadiazole-3-carboxamide;
- 25 N-[(S)-(4,4-difluorocyclohexyl)-[7-[[[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]methyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-(2,2,2-trifluoroethyl)-1,2,5-oxadiazole-3-carboxamide;

- 4-cyclopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-1,2,5-oxadiazole-3-carboxamide;
- 3-cyclopropyl-N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]isoxazole-4-carboxamide;
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-(difluoromethyl)-1,2,5-oxadiazole-3-carboxamide; and
- N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-(trifluoromethyl)-1,2,5-oxadiazole-3-carboxamide,
- or a pharmaceutically acceptable salt thereof.
12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent or excipient.
13. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.
14. Use of N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-methyl-1,2,5-oxadiazole-3-carboxamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating psoriasis.

15. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in therapy.
16. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable
5 salt thereof, for use in treating a disease or disorder selected from the group consisting of psoriasis, rheumatoid arthritis, spondyloarthritis, multiple sclerosis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis, hidradenitis suppurativa, systemic lupus erythematosus, palmoplantar pustulosis (PPP), atopic dermatitis, asthma, and/or COPD.
- 10 17. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the treatment of psoriasis.
18. A compound of N-[(S)-(4,4-difluorocyclohexyl)-[7-[(1S)-2-methoxy-1-[(4S)-2-oxo-4-(trifluoromethyl)imidazolidin-1-yl]ethyl]imidazo[1,2-b]pyridazin-2-yl]methyl]-4-
15 methyl-1,2,5-oxadiazole-3-carboxamide, or a pharmaceutically acceptable salt thereof, for use in treating psoriasis.